REMARKS

The Office Action of August 8, 2005, has been received and reviewed. Claims 1-17, 25-29, and 35-38 stand rejected. Claims 4, 17, 26, 35, and 36 are cancelled herein. Claims 1-5, 7-14, 25, 27-29, and 37 have been amended herein. Claims 1-3, 5-16, 25, 27-29, 37, and 38 are pending in the present application. All amendments and claim cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Elections and Restrictions

Applicants agree with the Examiner's statement, at page 2 of the *Office Action*, that "the elected group I, claims 1-17, 25-29, and 35-38 are under consideration." However, applicants respectfully submit that the Examiner's statement of "claims 3-34 and 36-52 are withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention," may have been an inadvertent error. *Id.* Applicants respectfully note that, in the Amendment filed October 4, 2001, applicants elected group I (*i.e.*, claims 1-17, 25-29, and 35) and added new claims 36-38. As such, applicants respectfully request that the statement asserting that "claims 3-34 and 36-52 are withdrawn" be withdrawn by the Examiner and that all of claims 1-3, 5-16, 25, 27-29, 37, and 38 be considered in the present application.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-17, 25-29, and 35-38 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. Claims 4, 17, 26, 35, and 36 have been canceled herein, rendering the rejections thereof moot. Applicants respectfully submit that the claim amendments overcome the remaining rejections and request withdrawal of the same.

Specifically, it was alleged that claims 1-17, 25-29, 35-38 were unclear as in what the metes and bounds of "functional derivative," "analogue," and "fragment" are. *Office Action*, at page 3. Although the applicants do not agree that any of these claims are indefinite, to expedite prosecution, the claims have been amended to remove "functional derivative," "analogue," and

"fragment" from the claims. As such, applicants respectfully submit that the rejections as to claims 1-3, 5-16, 25, 27-29, 37, and 38 under 35 U.S.C. § 112, second paragraph, have been overcome.

Furthermore, it was alleged that claim 5 was not clear in how the cell can be "primary" after it is transformed. *Id.* Applicants respectfully submit that because a sequence encoding at least one gene product of the E1 gene is present in the genome of a primary cell, this does not lead to the conclusion that the cell is transformed. The presence of a gene within a genome relates nothing about its ability to produce the protein it encodes. For example, a gene without the proper promoter and/or enhancer sequences would not lead to the production of the protein it encodes. Furthermore, the gene could be incorporated into a genome such that its expression is under the control of an inducible promoter. A cell would not produce the protein encoded by such a gene without the proper inducement. As such, applicants respectfully submit that one of skill in the art would recognize that just because a sequence encoding at least one gene product of the E1 gene is present in the genome of a primary cell, this does not lead to the conclusion that the cell is transformed. In light of the above, it would be apparent to one of skill in the art how a cell can still be considered "primary" after a sequence encoding at least one gene product of the E1 gene is caused to be present in the genome of a primary cell. Although the applicants do not agree that claim 5 is unclear, to expedite prosecution, claim 5 has been amended to remove "primary" from the claim. As such, applicants respectfully submit that the rejection of amended claim 5 under 35 U.S.C. § 112, second paragraph, has been overcome. Reconsideration of claim 5 is respectfully requested.

Last, it was alleged that claims 25-29 are not clear as they refer to "process" and that is not a statutory class of invention. *Id.* Applicants respectfully submit that a "process" is a statutory class of invention as provided by 35 U.S.C. § 101. To wit: "[w]hoever invents or discovers any new and useful *process*, machine, manufacture, or composition of matter, or any new and usefully improvement thereof, may obtain a patent therefore..." 35 U.S.C. § 101 (Emphasis added). As such, 35 U.S.C. § 101 specifically provides that a "process" is a statutorily patentable invention. As such, applicants respectfully submit that the rejections as to

claims 25, and 27-29 have no statutory basis under 35 U.S.C. § 101 and request withdrawal of the same.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-17, 25-29, and 35-38 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly lacking enablement. Claims 4, 17, 26, 35, and 36 have been canceled herein, rendering the rejections thereof moot. Applicants respectfully submit that the claim amendments overcome the remaining rejections and request withdrawal of the same.

Specifically, it was alleged that while the specification admittedly enables a method of growing influenza virus in a PER.C6 cell, it was not thought to reasonably provide enablement for "functional derivative," "analogue," "derived," and "fragment" of E1 and E2A or other viruses and other cell types. *Office Action* at pages 3-4.

Although the applicants do that agree that any of these claims lack enablement, to expedite prosecution, the claims have been amended to remove "functional derivative," "analogue," "derived," and "fragment" from the claims. As such, applicants respectfully submit that the rejections as to claims 1-3, 5-16, 25, 26-29, 37, and 38 under 35 U.S.C. § 112, first paragraph have been overcome.

Furthermore, it was alleged that growing influenza virus in a PER.C6 cell does not reasonably provide enablement for other viruses or other cell types. *Office Action* at page 4. Although the applicants do that agree that any of these claims lack enablement, to expedite prosecution, the claims have been amended to remove viruses other than influenza virus. Furthermore, applicants respectfully submit that the specification enables the production of influenza virus and/or influenza viral proteins in cell types other than PER.C6. All that is necessary for enablement is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. MPEP § 2164.08. Further, the scope of the enablement must only bear a "reasonable correlation" to the scope of the claims. *See, e.g., In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). It is well known by those of skill in the art that influenza viruses can infect a variety of primary and continuous cell lines. Schultz-Cherry et al., *Mink Lung Epithelia Cells: Unique Cell Line That Supports Influenza A and B Virus Replication*,

Journal of Clinical Microbiology, 36(12) page 3718 (1998). The Examiner's assertion that "influenza does not grow equally well in all cell types" does not mean that influenza does not grow at all in a variety of primary and continuous cell lines. Examples of influenza virus growing in human cells can be found in the scientific literature. For example, Endo et al. disclose the growth of influenza virus on human epithelial and fibroblast cells after 24 and 48 hours; Reina et al. disclose the growth of influenza virus in MRC-5, a human lung cell line. Endo et al., *Growth of Influenza A Virus in Primary, Differentiated Epithelial Cells Derived from Adenoids*, Journal of Virology, 70(3) page 2057, Fig. 2 (1996); Reina et al., *Comparison of Madin-Darby Canine Kidney Cells (MDCK) with a Green Monkey Continuous Cell Line (Vero) and Human Lung Embryonated Cells (MRC-5) in the Isolation of Influenza A virus from Nasopharyngeal Aspirates by Shell Vial Culture*, Journal of Clinical Mircobiology, 35(7) (1997). While applicants agree that some cells may be better than others for the production of influenza virus and/or viral proteins, this does not mean that a variety of primary and continuous cell lines are not enabled for such a purpose. As such, applicants respectfully submit that one of skill in the art would be able to practice the claimed invention in human cell types other than PER.C6 given the level of knowledge and skill in the art.

Furthermore, the fact that applicants do not provide examples for cell types other than PER.C6 does not mean that other cell types are not enabled by the disclosure. Not everything necessary to practice the invention need be disclosed. MPEP § 2164.08. In fact, what is well-known is best omitted. *In re Wright*, 27 USPQ2d 1520, 1513 (Fed. Cir. 1993). As such, the well known fact that influenza viruses can infect a variety of human cell types and produce influenza virus and/or influenza viral proteins need not be disclosed to enable the production of influenza virus and/or influenza viral proteins in cell types other than PER.C6. Consequently, applicants respectfully submit that the claims are enabled for the production of influenza virus and/or influenza viral proteins in human cells other than PER.C6. Therefore, applicants respectfully request that the enablement rejection under 35 U.S.C. § 112, first paragraph, be withdrawn and the claims reconsidered.

Claims 17 and 37 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly failing to comply with the written description requirement. Claim 17 has been canceled herein, rendering the rejection thereof moot. Applicants respectfully submit that the claim amendments overcome the remaining rejection and request withdrawal of the same.

Specifically, it was alleged that the specification provides an example of influenza virus and a cell type that is known in the prior art to grow adenovirus. *Office Action* at page 5. Furthermore, it was alleged that the specification does not provide enough examples from the list of viruses to provide written support for the list of viruses claimed. *Id.* Last, it was alleged that the specification does not provide examples of the chromatographic columns and methods needed to purify the range of viruses. *Id.*

Applicants respectfully submit that adequate written description is provided in the specification to support amended claim 37. Amended claim 37 is directed to a method of purifying influenza virus or influenza viral protein from a cell having a plasmid comprising an Ad serotype 5 (Ad5) E1A- and E1B-coding sequence (Ad5 nucleotides 459-3510). The specification, at page 6, lines 16 through 21 provides that "PER.C6 cells were generated by transfection of primary human embryonic retina cells, using a plasmid that contained the Ad serotype 5 (Ad5) E1A- and E1B-coding sequences (Ad5 nucleotides 259-3510) under the control of the human phosphoglycerate kinase (PGK) promoter." As the specification clearly recites the elements present in amended claim 37, applicants respectfully submit that claim 37 is supported by adequate written description in the specification. As such, applicants respectfully request withdrawal of the rejection of claim 37 under 35 U.S.C. § 112, first paragraph, and reconsideration of the claim.

Claim 13 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly no providing adequate disclosure for the claim. Specifically, it was alleged the claim requires a specific deposited cell and that deposit of the cell would satisfy the enablement requirements of 35 U.S.C. § 112. *Office Action*, at page 6. As is noted in amended claim 13, a PER.C6 cell is represented by the cells deposited under ECACC no. 96022940. The ECACC has been established as a recognized IDA Patent Depository since 1984 under the Budapest Treaty (1977). It accepts cell lines, viruses, bacteria and DNA for deposit. As such, applicants respectfully submit that a

deposit has made under the terms of the Budapest Treaty. In addition, provided herewith, is the required statement under the terms of the Budapest Treaty signed by Dr. Ronald Brus of Crucell Holland BV. Crucell Holland BV is the current assignee of the present application as established by the enclosed Change of Name of Assignee, a copy of which has been forwarded to the recording office. As such, withdrawal of the rejection and reconsideration are respectfully requested.

Rejections under 35 U.S.C. § 102(b)

Manservigi et al.

Claims 1-3, 5, 6, 14, 15, 17, 25, and 38 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Manservigi et al. Claim 17 has been canceled herein rendering the rejection thereof moot. In light of the amendments to the claims, withdrawal of the remaining rejections and reconsideration are respectfully requested.

Specifically it was alleged that Manservigi et al. teach the production of a viral glycoprotein (HSV bB) in 293 cells. *Office Action* at page 7. Further, it was though that 293 cells are immortalized with the E1 region of adenovirus 5; the cells produce no adenoviral structural proteins; and that 293 cells contain part of pIX but it has been shown not to produce that protein. *Id.* Although the applicants do not agree with the Examiner's characterization of the teachings of Manservigi et al. with respect to the present application, claims 1-3, 5, 14, and 25 have been amended to expedite prosecution. Specifically, amended claims 1 and 25 now, in part, recite "wherein said cell is a human embryonic retinoblast," and "infecting said cell with an influenza virus." In addition, claim 1 now further recites "allowing for expression of said influenza virus and/or influenza viral proteins," and "harvesting said influenza virus and/or influenza viral proteins."

A claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants respectfully submit that amended claims 1 and 25 cannot be anticipated by Manservigi et al. as this reference does not teach each and every element of amended claims 1 and 25. Specifically, Manservigi et al. does

not teach the use of a human embryonic retinoblast or infecting a cell with an influenza virus. As such, Maservigi et al. cannot anticipate claims 1 and 25. Furthermore, as to claim 1, Manservigi et al. do not teach expressing or harvesting influenza virus and/or influenza viral proteins. As such, claim 1 is further patentable over Manservigi et al. as it does teach these elements of claim. In light of the foregoing, applicants respectfully request the withdrawal of the rejections of claims 1 and 25 and reconsideration.

Furthermore, applicants respectfully submit that claims 2, 3, 5, 6, 14, 15, and 38 cannot be anticipated by Manservigi et al. because, at the very least, they depend either directly or indirectly from claim 1, and amended claim 1 is not anticipated by Manservigi et al.

WO 97/00326 to Fallaux et al.

Claims 25-29 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by WO 97/00326 to Fallaux et al. Claim 26 has been canceled herein rendering the rejection thereof moot. In light of the amendments to the claims, withdrawal of the remaining rejections and reconsideration are respectfully requested.

Specifically it was alleged that the claims were not clear if they were a product or a method because there are no positive method steps and the claims recite qualities of a product; the claims were therefore treated as product claims. *Office Action* at page 7. Furthermore, it was alleged that WO 97/00326 teaches a cell that expresses E1 and E2 (ts and normal) that is derived from a primary cell and is a clone called PER.C6. *Id.*

Applicants respectfully submit, that claim 25, as amended, recites positive process steps (*i.e.* "culturing" and "infecting") and should be treated as a process. Furthermore, the preamble of claim 25 has been amended to be no longer directed to "an improvement," but is now more clearly directed to "a process." As such, applicants respectfully request that claim 25 be examined as a process.

In addition, a claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros.* at 1053. Applicants respectfully submit that claim 25 cannot be anticipated by WO 97/00326 as this reference does not teach each and every element of amended claim 25. Specifically, WO

97/00326 does not teach the use of a human embryonic retinoblast or infecting a cell with an influenza virus as recited in amended claim 25. As such, WO 97/00326 cannot anticipate amended claim 25. In light of the foregoing, applicants respectfully request the withdrawal of the rejection of claim 25 and reconsideration.

Furthermore, applicants respectfully submit that claims 27-29 cannot be anticipated by WO 97/00326 because, at the very least, they depend either directly or indirectly from claim 25.

U.S. Patent 5,518,913 to Massie et al.

Claims 1-3, 5, 6, 14, and 15 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by U.S. Patent 5,518,913 to Massie et al. Specifically, it was alleged that the claims are drawn to a method of producing a viral protein (that is not adenoviral) in a cell with an E1 gene or function. *Office Action* at page 8. Further, it was alleged that the claims do not exclude the use of adenoviral vectors because the claims are drawn to producing a non-adenoviral virus or non-adenoviral protein and also wherein the cells do not produce adenoviral structural proteins. *Id.* Last, it was alleged that Massie et al. teach production of a transgene in a cell (293) immortalized with the E1 region of adenovirus 5 that produces no adenoviral structural proteins and that the transgenes were isolated and examined for the amount of transgenic protein produced. *Id.*

A claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros.* at 1053. Applicants respectfully submit that amended claim 1 cannot be anticipated by Massie et al. as this reference does not teach each and every element of amended claim 1. Specifically, Massie et al. do not teach the use of a human embryonic retinoblast, infecting a cell with an influenza virus, or expressing or harvesting influenza virus and/or influenza viral proteins. As such, Massie et al. cannot anticipate amended claim 1. In light of the foregoing, applicants respectfully request the withdrawal of the rejection of claim 1 and reconsideration.

Furthermore, applicants respectfully submit that claims 2, 3, 5, 6, 14, 15 cannot be anticipated by Massie et al. because, at the very least, they depend either directly or indirectly from claim 1, which is not anticipated by Massie et al.

U.S. Patent 6,855,544

Claims 1-17, 25-29, 35-38 stand rejected under 35 U.S.C. § 102(e) as assertedly being anticipated by U.S. Patent 6,855,544 ("the '544 patent"). Claims 4, 17, 26, 35, and 36 have been canceled herein, rendering the rejections thereof moot. Applicants respectfully submit that the claim amendments overcome the remaining rejections and request withdrawal of the same.

Specifically, it was alleged that the claims are drawn to producing non-adenovirus or proteins in a cell containing E1 and/or E2. *Office Action* at page 9. Further, it was alleged that both set so f claims are based on using PER.C6 cells to produce non-adenoviral proteins, and that PER.C6 cells comprise the E1/E2 regions and variants thereof.

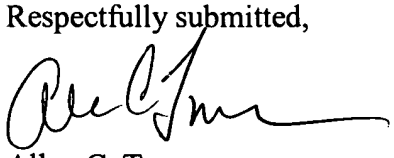
A claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros.* at 1053. Applicants respectfully submit that claims 1 and 25 cannot be anticipated by the '544 patent as this reference does not teach each and every element of amended claims 1 and 25. Both amended claim 1 and amended claim 25 recite "infecting said cell with an influenza virus." While the '544 patent does teach the use of adenoviruses to infect cells, it does not teach the infection of cells with an influenza virus. As such, applicants respectfully submit that the '544 patent cannot anticipate amended claims 1 and 25. In light of the foregoing, applicants respectfully request the withdrawal of the rejections of claims 1 and 25 and reconsideration.

Furthermore, applicants respectfully submit that claims 2-12, 14-16, 27-29, 37, and 38 cannot be anticipated by U.S. Patent 6,855,544 because, at the very least, they depend either directly or indirectly from amended claim 1 or amended claim 25, which are not anticipated by the '544 patent.

CONCLUSION

Claims 1-3, 5-16, 25, 27-34, 37, and 38, as amended, are believed to be in condition for allowance, and notice thereof is respectfully solicited. Should the Examiner determine that additional issues remain which might be resolved by a telephone conference, he is respectfully invited to contact Applicants' undersigned attorney.

Respectfully submitted,



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